Biosimilars in Emerging Markets
Is It A Level Playing Field?

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EXECUTIVE SUMMARY

Governments, healthcare payers, and social and health reforms, combined with the increased incidence of conditions such as cancer and diabetes are paving the way for increased uptake of biologic medicines in emerging markets. However, expensive biologic medicines can be prohibitive to many patients, creating a high level of unmet clinical need. At its best, the global expansion of biosimilars can mean a robust and steady supply of existing and new drugs reaching far-flung patient populations, but localized biosimilar drug developments, especially in China and India, combined with a lack of robust pharmacovigilance systems, threaten to derail the industry by putting patient health at risk.

It’s a chilling fact: One irresponsible company could seriously damage, or even destroy the biosimilar field. A single company cutting corners with under-regulated, lower-quality development could create an inferior product that harms or kills patients. In that instance, news media reports marked by huge headlines might quickly focus on the entire biosimilar
industry instead of a single company. The results would be devastating for the industry as a whole and the patients who benefit from its accessible, and generally much-less expensive products.

Regulators across the globe have a duty to ensure the sustainability of biosimilars.

**DEFINING BIOSIMILARS**

Before reviewing the new market situation and offering possible solutions, it’s important to clear up the widespread confusion concerning the basic definition of biosimilars. We define them here as copy biologics, with a clear and effective regulatory route of approval that requires comparability studies against the originator reference product at all stages of development — quality, non-clinical, and clinical.

Harmonized definitions are of critical importance because any “fuzziness” can confuse people outside of the industry when published reports are mistakenly construed as a criticism of biosimilars. In many cases, they are talking about something else, such as follow-on biologics that did not undertake stringent comparability and bioequivalence studies, otherwise called non-original biologics (NOBs). We all need to employ, and understand, the same terminology.

**THE REGULATORY PICTURE BEGINS TO FOCUS**

Due to the complex nature of biologic medicines, biosimilar development is highly regulated. EMA, FDA, and WHO have published guidelines, and while there are some minor differences, overall they all require comprehensive comparability exercise to the originator: quality, non-clinical, and clinical. The cost can be high, and the time to complete the program can be long. Most of the pharma-emerging countries have also developed, or are in the process of developing, their own regulatory pathway for the approval of biosimilars. While the concept is similar to the European and WHO framework, in certain countries the barrier is lower to enable a lower cost of development and a shorter time to market, creating something of a tangled contradictory mess with some companies adapting generic-like pathways.
THE BIOSIMILAR MARKET SPREAD

The biosimilar market has expanded significantly in the last few years; however, it’s over the next 10 years that we will witness a truly transformative change. China, India, Brazil, and Russia, among others, already have one toe in the marketplace, but they are about to dive in and change everything. Each of those markets is huge. Under current conditions, parochial clinical trial requirements, and an uneven regulatory playing field would force many outside companies to establish separate divisions simply to develop biosimilars in China and many other countries. In the vast majority of cases, that’s simply not economically viable. The future success of biosimilars is not dependent on the US and Europe alone. The need is greatest in Asia, and this market will influence the worldwide situation and be the fastest to adopt biosimilars. Drivers for fast uptake include low clinical development cost, unhindered product launches due to a different patent landscape, cheap workforce, less stringent regulatory framework, and therapy primarily chosen by physicians.

Before looking into the crystal ball, it’s important to have a clear perspective on market realities in 2 of the largest potential biosimilar marketplaces: China and India.

A Closer Look: China

In October 2014 China’s Center of Drug Evaluation (CDE) published draft guidance for approval of biosimilars. CDE, which is part of the China Food and Drug Administration (CFDA) (simplified Chinese: 国家食品药品监督管理总局) – the Chinese authority that oversees all drug manufacturing, trade, and registration in the country – has released the draft guidance for a one-month consultation period.

The new draft guidance establishes the basic principles of the research, development, and evaluation of a biosimilar drug by outlining the need for comparability, a step-wise approach to testing, consistency of the drug samples used, and the necessary clinical studies required to support the evaluation of similarity. A step-by-step procedure in which “no or little difference” in comparability testing is found, could allow subsequent comparability tests to be skipped. The guidance is applicable to well-characterized therapeutic recombinant proteins with clear functions.

The draft guidance defines biosimilars as therapeutic biological products that are similar to the reference drugs in terms of quality, safety, and efficacy, and that have the same amino acid sequence. The reference drugs have to be an originator biological approved in China. The draft guidance also allows for extrapolation of indications, which will be considered on a case-by-case basis.

Though guidelines are forthcoming, the situation in China is thorny and complex.
The biggest uncertainty in China is the review process. Put simply, problems abound. For starters, there are not enough qualified regulatory staff in this giant nation. The product approval backlog is daunting for any company considering market entry. It can take 18 months for approval of a clinical trial there, compared to 30 days in the US. Further complicating matters are local issues, as Chinese regulatory officials want clinical trials to be conducted in China. Whilst this makes sense if there is a specific ethnicity issue, it makes no sense for all trials to be run there.

In the vast majority of cases, biosimilars already possess a slew of documentation attesting to their safety. We don’t need to reinvent the wheel in most biosimilar clinical trials. Obviously, adhering to these requirements would hike the costs of trials. Market delays could very well be the reality. Furthermore, these uncertainties are even greater for non-Chinese companies unfamiliar with the country’s regulatory nuances, putting local companies at an advantage. Outside companies will be hard pressed to economically justify operating in China. Worse, China will then depend too much on smaller Chinese manufacturers with lower production capabilities, which will hamper any globalization efforts.

There are many approved so-called “biosimilars” in China from local manufacturers. What will be their status? Will the term “biosimilars” be rejected as they have not gone through the new biosimilar regulatory pathway? It is unlikely that the CFDA will retract any names, which only adds to the confusion as new products are licensed under the biosimilar pathway creating 2 tiers of biosimilars in the market place.

Technically the draft does not have any legal effect. It is unclear whether companies can file under the new designation, or have to wait until the guidelines are final, which could take years. As the guidelines reflect “updated standard of thinking” and China’s government has publicly said it desires biosimilars to reduce healthcare expenditures, one would expect the draft guidelines to be used.

**A Closer Look: India**

Department of Biotechnology (DBT) and Central Drugs Standard Control (CDSCO) issued a biosimilar guideline in June 2012. The concept is similar to that of the EU, US and WHO. The development follows a step-wise approach with extensive quality characterization, a detailed requirement for animal studies, and clinical requirements. But digging deeper, there is a potential for reduced clinical package and waiver of safety/efficacy clinical studies. Reference product should be licensed in India, and if not, it must have at least 4 years of use in a highly regulated market. India also requires locally generated clinical data.
There are several approved biosimilars in India from local companies; the majorities were approved prior to the release of the biosimilar guidelines. The data packages are minimal with limited comparability undertaken. Dr Reddy’s biosimilar Rituximab was licensed with data from a non-comparative open-label study in 68 patients, compared with ongoing biosimilar Rituximab studies that include hundreds of patients. It is arguable that the approval of Dr Reddy’s Rituximab is prior to the release of the biosimilar guidelines; however, a more recent example is biosimilar Infliximab which is licensed in the EU and India. Celltrion submitted data on 856 subjects (phase I and III) for the EU registration, while Epirus only submitted data on 273 subjects (phase I and III) for a license in India.

Sample size is driven by the need to establish biosimilarity rather than clinical benefit (already established by the reference product) and typically depends, for efficacy, on non-inferiority designs and their associated issues. These include the chosen primary endpoint, the time to measure the endpoint, establishment of an acceptable non-inferiority (or equivalence) margin, taking into account relevant historical data and clinical considerations, and adequate powering. It is evident that there is a difference between the Celltrion Infliximab and Epirus Infliximab clinical packages that was submitted for licensing, indicating a difference in expectations from different regulatory agencies.

All products approved as biosimilars prior to the guidelines and post guidelines retain the “biosimilar” designation creating 2 tiers of biosimilars, just like in China. Lack of robust pharmacovigilance systems makes it virtually impossible to track and trace adverse events.

**NEW IDEAS FOR A BETTER FUTURE**

The regulation frameworks are inconsistent with global norms and can expose patients to unknown risk. Adapting generic-like pathways to approve biosimilars is dangerous.

Clinical trials are expensive. A reduction of the clinical package is what regulators across the globe are keen to explore to avoid any unnecessary exposure of patients to trials. However, the science of biosimilars must be preserved in order to give confidence to the users. This is further compounded by the lack of robust pharmacovigilance systems in emerging markets which hinders signal detection. The uncertainties between regions only serve to confuse the users and create divergence.

The solution is relatively simple; it’s the getting there that could prove to be the hard part. Agencies must find ways to work together and ultimately harmonize the
biosimilar pathway. Once hammered out, agencies would need to codify them into a unified set of guidance that spell out in some detail the design requirements for patient population, endpoints, acceptability margins, immunogenicity testing, and extrapolation requirements. Systems and processes should be put in place for effective tracing of adverse events globally. Post-marketing safety studies should be mandatory.

Diligence is critical as we see expansion in the uptake of biosimilars in these 2 giant markets.

CONTACT INFORMATION

For further information, or to discuss any aspect of PRA’s services offered in the field of biosimilars trials, please contact your PRA Account Director or the PRA employee below:

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